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November 9, 2004

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Subject: Docket No. 2004P-0074 - Statement in Support of the Citizen Petition filed by Savient Pharmaceuticals

Dear Sir or Madam:

Enclosed are an original and three duplicate copies of an expert statement in support of Savient Pharmaceuticals Inc.'s Citizen Petition regarding interactions between oxandrolone and warfarin.

Best regards,

Edward John Allera
Donald E. Segal
Theodore M. Sullivan

2004P-0074

Enclosure

SUP2

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WARFARIN/OXANDROLONE INTERACTION IN ELDERLY PATIENTS

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The University of Michigan
Ann Arbor, Michigan

Respectfully submitted:

Manju T. Beier, Pharm D., FASCP
10/27/04

Background: professional practice and experience

I'm senior partner with Geriatric Consultant Resources LLC (http://www.gcrweb.com); a company specializing in the education and research needs of pharmacists, physicians, and other health care professionals responsible for providing pharmacotherapy to older adults. I also hold an academic appointment as Clinical Associate Professor of Pharmacy at the University of Michigan, Ann Arbor, Michigan. My clinical practice involves older adults in long-term care, and ambulatory settings.

I have 17 years of practice as a pharmacist in geriatric pharmacotherapy and medication management in older adults in long-term care and community based-living. I have given numerous seminars and workshops addressing geriatric pharmacotherapy on a local, state, national, and international level.

I am actively involved with the American Society of Consultant Pharmacists (ASCP) and have recently served two terms on the Board of Directors. I have chaired the Society's Education Advisory Committee for 2002-03. My most recent appointment is to chair the Society's Evidence-Based Medicine Task Force for 2003-04. In 1996, I was recognized by the Society with the ASCP/Eli Lilly and Company Leadership in Education Award.

I currently serve on the editorial board of several journals related to geriatrics and aging and psychopharmacology including *Journal of Gerontology-Medical Sciences, Geriatric Times, CNS-LTC, ElderCare* and *The Consultant Pharmacist.* I have been invited by the American Medical Directors Association to serve on Clinical Practice Guideline Panels addressing Management of Heart Failure, Pharmacotherapy of Depression, Osteoporosis and Falls, and Alzheimer's Dementia in the nursing home elderly.

I am also an invited member of the Michigan Dementia Coalition, a group representative of researchers, educators, and health care professionals managing dementias in Michigan.

The Geriatric Population

The elderly population, especially the chronically sick and frail adults that reside in skilled nursing facilities are the most vulnerable segment of our society in terms of therapeutic misadventures and adverse drug experiences. As we age, pharmacokinetics and pharmacodynamics of drugs are profoundly altered, and it takes special care to ensure that drug therapy is optimized to achieve the best possible outcomes.

Since the nursing home elderly receive on an average of 7 medications, they are especially prone to drug-drug and drug-disease interactions. The entire healthcare team in long-term care depends on the expertise of the pharmacist to monitor drugs keenly in hopes of avoiding and preventing adverse drug experiences.

Warfarin and INR's

Warfarin is a narrow therapeutic index drug and has the propensity for many drug-drug interactions and requires scrupulous monitoring to ensure that the International Normalized Ratio ("INR"), a standardized measure of coagulation, is within therapeutic range, usually between 2-3, as recommended by the guidelines for many of its indications. The elderly are especially sensitive to a large number of factors that can cause unsafe high or low INR levels.

Warfarin has long been recognized as a drug prone to causing clinically significant drug-drug interactions. Most of these interactions are recognized as resulting from the second drug interfering with warfarin's strong tendency to bind albumin, a protein that circulates in the blood. Approximately 99% of the warfarin that is measured in a plasma sample is attached to albumin. Only the remaining unbound 1% of the circulating warfarin is actually available and able to diffuse into liver cells (where it manifests its effect on coagulation factors) as blood circulates through the liver. If a second drug is administered that reduces the number of albumin binding sites available to warfarin, the amount of "free" warfarin increases, which then increases the amount of warfarin available to enter the liver cells. A small change in the amount of protein binding, e.g. from 99% to 98%, can have a dramatic effect on the amount of free warfarin available, e.g. doubling the concentrations from 1% to 2%.

In addition to the potential for drug-drug interactions, the literature points to substantial interpatient and intrapatient variability in anticoagulation effect with warfarin, especially in the elderly. Prescribers and pharmacists must devote considerable time to ensure that the patient is not at risk for bleeding because of increased INRs, or at risk of thrombosis because of sub-therapeutic INR levels.

Several factors that potentially affect INR during warfarin dosing:

1) Elderly patients reach steady state more slowly than the younger, healthy volunteers that commonly participate in clinical studies of drugs. Elderly patients often take up to 2 weeks to reach steady state with warfarin after a dosage change (not the 3-5 days that is found the literature) especially when therapy is initiated. Prior history of stability on a previous dose needs to be factored in when determining dosage changes. With any change in dosage to adjust the INR, 2-3 days may be needed for a new INR to emerge.

2) Thyroid problems (hypo or hyper) can affect INR due to clearance rate of clotting factors. Changes in INR may continue to occur within a 30-day period as levels change in the body and the thyroid function is stabilized.

3) Changes to other medications will necessitate close monitoring of INR. Caregivers must be aware of any medications that have been started, stopped, increased or lowered within the last 2-4 weeks that may affect warfarin disposition.

4) Diet (green leafy vegetables) and commercial nutritional supplements (such as Ensure) can be a significant source of vitamin K. Taking 3 cans per day of a

supplement rich in vitamin K can significantly impact INRs and consequently the dosing of warfarin.

5) Low serum albumin: since warfarin is highly protein bound, decreased albumin levels typically require lower doses of the drug to achieve the target INR. As nutritional status improves, a given dose may be less effective as it becomes bound by more of the albumin. Some patients with poor liver function have low albumin which can affect the output of clotting factors and hence INR levels.

6) Fluid status changes affect INR and the elderly are especially prone to subtle fluid changes in the system because of diseases and environmental factors.

7) Constipation or diarrhea can potentially affect INR's. When an older adult is constipated (frequent occurrence in this population) food stays in the gut a longer time potentially increasing vitamin K absorption. If a patient develops diarrhea, the INR can go up or down depending on the timing of the diarrhea and the warfarin dosing. There can be the loss of a dose of warfarin if diarrhea occurs soon after having taken the drug, or diarrhea can cause loss of vitamin K absorption.

8) Patients who lose or gain 10 pounds may need less or more warfarin with these weight changes. Care must be taken to determine whether this is just fluid or true weight loss.

In essence for warfarin dosing, the three D's need to be considered every time for any changes to explain fluctuations in INR:

- Diet: any increase or decrease, change in quantity or quality of the foods regarding vitamin K content must be evaluated.
- Drugs or medications (prescription and OTC and herbals): anything stopped, started, increased or lowered must be considered.
- Disease or illness: a fever can metabolize clotting factors faster, congestive heart failure, thyroid disease, renal failure, ascites, all need to be factored into the equation.

Educating patients, family and caregivers to be reliable sources of information is important to the decision-making process, and is essential for making wise decisions to minimize risks and maximize benefits of warfarin therapy. It is indeed a challenge to maintain the INR within the target therapeutic range given all the factors that potentially affect warfarin disposition.

Oxandrin and Warfarin Interaction

The pharmacological mechanism by which oxandrolone acts to affect the potency of warfarin therapy has not yet been investigated. The obvious hypothesis is to assume that oxandrolone, like many other drugs, interferes with the protein binding of warfarin leading to increased concentrations of free warfarin and increased anticoagulant activity. Other possible reasons, such as inhibition of drug metabolism, have been suggested.

Whatever the cause, the effect can be counteracted clinically by reducing the warfarin dose, as was shown to be effective in the recently concluded Oxandrin study.

Formulary/pharmacy practice in long-term care facilities

Nursing facilities largely contract with large pharmaceutical (institutional pharmacies) companies to provide their dispensing and consulting pharmaceutical services.

- The decision to stock which version of a certain drug on the company's formulary is a fluid one and is dictated by contract price, availability, clinical effectiveness, safety and other factors.
- The physician and/or the administering nurse would most likely not be aware of a switch from Oxandrin to a generic version for example, or between two generics. On the contrary, if oxandrolone were a narrow therapeutic index ("NTI") drug, such a change would be more carefully monitored and its potential impact well noted and communicated to the nursing and medical staff by the pharmacy.

Conclusion

In my estimation, any generic oxandrolone should be required to demonstrate, by clinical trial, the degree of interaction with warfarin to minimize the variability that can occur with dosing. As has already been described, a multitude of factors affect warfarin dosing especially in the frail elderly. An 80-85% dosage reduction in warfarin when a patient is on Oxandrin is a dramatic change in dosing to reduce adverse experiences, such as bleeding. This becomes yet another factor to consider in an already complicated drug and disease-interaction environment. To introduce further complicating factors, such as the possibility of different degrees of effect on warfarin interaction when changes are made in the patient's oxandrolone from brand to generic, or from one generic to another, represents a significant safety risk. To minimize this new variable and potential risk, the bioequivalence of generic oxandrolone drug products should be demonstrated through clinical studies demonstrating an impact on warfarin dosing, as well as through traditional bioequivalence measures.